Remarks

Claims 1 and 15-28 remain pending and under consideration. Applicant has amended claims 1, 26 and 27. No new matter is added by virtue of the amendments contained herein. Support for the amendments lies in the original claim 1 and specification as filed. Applicants responds fully to each of Examiner's rejections as follows.

Double Patenting

The Examiner advised Claim 28 will be objected to under 37 CFR 1.75 as being a substantial duplicate of Claim 22 should Claim 22 be found allowable.

The Examiner advised Claim 26 and Claim 27 will be objected to under 37 CFR 1.75 as being a substantial duplicate of Claim 1 should Claim 1 be found allowable.

The Examiner advised Claim 21 will be objected to under 37 CFR 1.75 as being a substantial duplicate of Claim 20 should Claim 20 be found allowable.

Applicants appreciate the Examiner's advisement, and respectfully submit any or all of the above objections will be addressed and/or explained as to the improper objection accordingly upon indication of allowability of the Claims.

Specification

The Examiner objected to the disclosure because of recitation of U.S. Provisional Application 60/009,293 on page 1, line 4.

The Examiner objected to the amendment filed 10-17-03 as introducing new matter for the recitation of the phrase "all of which are herein incorporated by reference in their entirety".

Applicants have amended the Related Applications paragraph which was objected to correct the inadvertent typographical error reference in the provisional application serial number, and to incorporate by reference only the pending parent application. Since the incorporation by reference statement was filed at the time of filing the application, no new matter is added by virtue of this statement. It is believed the present amendments render the objections moot. Withdrawal of the objections is respectfully requested.

Indefiniteness

The Examiner has rejected claims 1 and 15-28 under 35 USC § 112 as being incomplete for omitting essential steps, amounting to a gap between the steps. The Examiner maintains the omitted steps are: where the pharmaceutical composition is administered to; how the pharmaceutical composition is administered, and whether the neuroectodermal tumor has been treated or whether the symptom of the neuroectodermal tumor is ameliorated by treatment. Applicants respectfully traverse the rejection.

Applicants submit the present requirement of the Examiner is misplaced and unduly burdensome and limiting in the present instance. The purpose of the requirement under 35 USC §112 second paragraph, is to ensure that the scope of the claim is clear so as to inform the public of the metes and bounds of what is claimed, and to provide a clear measure as to what applicants regard as the invention. See MPEP2173. Furthermore, Applicants submit the breadth of a claim should not be equated with indefiniteness unless the scope of the claim is unclear or if applicants have indicated the invention to be of a scope different than from that defined by the claim. If the claim is clear, a rejection under 35 USC 112, second paragraph is undue. See MPEP2173.04.

However, solely in an effort to address any concern of the Examiner, and without prejudice disclaimer or waiver, Applicants have amended Claim 1, Claim 26 and Claim 27 to recite administration of the composition is "to an individual having a neuroectodermal tumor, wherein administering the composition results in treatment of the tumor." Reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph is respectfully requested.

Enablement

The Examiner has rejected claims 1 and 15-28 under 35 USC § 112 as failing to comply with the enablement requirement. The Examiner maintains the specification fails to provide adequate guidance and evidence for how to treat a neuroectodermal tumor, such as ependymomas, medulloblastoma, pheochomocytoma, glioblastoma, neuroblastoma, or any metastatic tumors of neuroectodermal origin in the brain, by using a pharmaceutical composition comprising a chlorotoxin fused to a cytotoxic moiety such as gleonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin, or any complement protein via various administration routes in vivo. Applicants respectfully traverse the rejection.

The Examiner asserts the claims read on protein therapy in vivo and questions the unpredictable nature of protein therapeutics. In his remarks, the Examiner relies on arguments and supporting articles which discuss challenges associated with gene therapy. Applicants respectfully disagree with the Examiner, and point out protein and peptide biotherapeutics have been approved and used as successful

therapies for many years. For example, recombinant insulin was approved for use in 1982, erythropoietin was approved for use in 1989, and the first monoclonal antibody (Muronomab (anti-CD3)) was approved for use in 1986. Furthermore, non-recombinant purified protein such as insulin have been utilized as early as 1922 in therapeutic applications. Additionally, numerous additional protein therapeutics have been approved for therapies, further supportive of the premise that the concerns of gene therapy and protein therapy are not in fact directly parallel; and the idea that gene therapy is unpredictable is not properly translated as supportive that protein therapeutics are similarly unpredictable.

Applicants submit the Examiner's focus on gene therapy and questions arising out of any unpredictability of gene therapy as effective therapeutic use does not apply in the present circumstance. The Examiner's cited articles discuss the difficulties of effective introduction of vectors into cells for protein production, difficulties of protein production in cells, and difficulties of effective protein secretion from cells for delivery throughout the individual. Applicants' claims are directed to methods of treating an individual having a neuroectodermal tumor by administering a protein biotherapeutic (e.g., chlorotoxin fused to a cytotoxic moiety) and compositions containing protein biotherapeutics. Whereas the difficulties of gene therapy are certainly understood, the same concerns do not transfer directly to protein therapeutics, as evidenced by the years of successful approved therapies (discussed above). In the event the Examiner maintain any rejection supported by this assertion, clarification is respectfully requested.

Additionally, the Examiner asserts the specification fails to provide adequate guidance and evidence for various administration routes due to the presence of the blood brain barrier , and stability of a protein. Applicants submit determination of effective doses, protein half life, and delivery is routine procedures which would not require undue experimentation by one skilled in the art. Furthermore, Applicants submit herewith in the Appendix an abstract publication of Veiseh, et al., demonstrating that the presence of the blood brain barrier does not pose a particular challenge for chlorotoxin fusions. In fact, IV administration of chlorotoxin fusions are effectively and specifically delivered to brain tumor sites in the absence of surgical disruption of the blood brain barrier. See Veiseh, et al., "Tumor Paint: A chlorotoxin based biomarker for intra-operative imaging of cancer foci." *Nanotech 2006 Conference.* May 7-11, 2006. Abstract. Thus, the assertion of the Examiner that chlorotoxin and chlorotoxin fusions would not pass the blood brain barrier is not properly based.

Finally, the Examiner refers to the predictability of changes in amino acid sequences, citing Kaye et al., which discusses changes in proteins with known activities which result in changes in functional activity as well as Davis and Skolnick, which discuss diverse families of molecules having varied functional activities as supportive of the premise that various combinations of cytotoxins and chlorotoxin

may vary dose, stability and effect of cytotoxic moiety in vivo so as to be non-enabling. Applicants respectfully disagree.

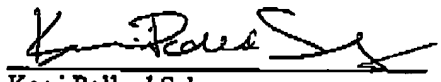
Again Applicants submit the Examiner's focus is misplaced. Applicants point out Kaye, Davis and Skolnick are directed to concerns relating to prediction of function of proteins with various sequences which are related at various degrees, and a lack of immediate correlation between sequence and function in the absence of additional characterization or understanding about a protein. Applicants clarify the present claims are directed to methods of using a composition comprising a fusion of chlorotoxin (having known sequences and known function) with a moiety known to be a cytotoxin (having known sequences and known function). Applicants submit the combination of chlorotoxin fused to a cytotoxic moiety is within the realm of nothing more than routine experimentation of one skilled in the art. In view of Applicants' teaching, one skilled in the art would be well equipped to make and use the methods as claimed using only routine testing and experimentation.

A specification disclosure which contains a teaching of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented is presumably in compliance with the enablement requirement, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In order to make an effective enablement rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, supported by reasons why the truth or accuracy of enablement is questioned, and by evidence which is inconsistent with Applicants' contested statement(s). See MPEP 2164.04. Applicants submit the statements and support relied on by the Examiner in the present rejections are misplaced and not supportive of an effective *prima facie* case of lack of enablement. For this and all of the reasons discussed above, the rejection under 35 USC §112 first paragraph should not be maintained. Reconsideration and withdrawal of the rejection is thus respectfully requested.

In summary, Applicant respectfully submits that the present case is in condition for allowance. Should the Examiner maintain that some of the issues addressed herein remain unresolved, the undersigned would appreciate the opportunity to discuss such issues at the Examiner's convenience and hereby requests an Examiner interview by telephone for this purpose.

A petition for a three (3) month extension of time and American Express credit card form to cover the fee for an extension of time are enclosed. It is believed no additional fees are due in association with filing of these papers, however, in the event any additional fees are due, please charge any additional fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,



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[redacted]

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Tumor Paint: A chlorotoxin-based biomarker for intra-operative imaging of cancer foci

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Fred Hutchinson Cancer Research Center, US

Keywords:
cancer diagnosis, cancer trageting, chlorotoxin, near infrared imaging

Abstract:
Recent advances in molecular biology and nano-medicine have improved early tumor detection through recognition of molecules that are specifically expressed in malignant cells. This has the potential to specifically "paint" tumors with targeted molecular probes. In this view, we developed and characterized a near infrared (NIR) chlorotxin-based probe to detect and paint cancer cells in vitro, in vivo and ex vivo. We demonstrate the exquisite delineation of malignant brain cells (glioma and medulloblastoma) from normal brain tissue after systemic administration of the probe in 2 mouse models. The medulloblastoma tumors were formed in the absence of surgical disruption of the blood brain barrier and their NIR signal were detected through intact skull and scalp. The broader utility of the probe was demonstrated through ex vivo and in vivo imaging of adenocarcinoma, rhabdomyosarcoma and spontaneous prostate cancer mice models. Results showed that it could specifically demarcate primary tumors and cognate lung and lymphatic metastases as small as 1.5 mm in diameter. Biodistribution and toxicity studies indicated favorable properties for advancement to human trials. This probe has potential to improve not only intraoperative tumor detection and resection but also diagnosis and imaging of various malignancies.

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Nanotech 2006 Program - Tuesday May 9

8:30 Keynote - Sensors & Systems: MEMS & NEMS, MSM Roon
Session chair: Elena Gaura, Coventry University, UK
8:30 Nano Electromechanical Devices: Opportunities and Challenges (invited)
R.T. Howe, *Stanford University, US* (speaker biography)
9:15 A Designer's Guide to CMOS MEMS (invited)
G.K. Fedder, S. Simone and N. Sarkar, *Carnegie Mellon University, US* (speaker biography)

8:30 Keynote - Soft Nanotechnology: Characterization Roon
Session chair: Fiona Case, Case Scientific, US
8:30 Colloidal Delivery Systems for Functional Food Design (invited)
K. Velikov, *Unilever R&D, UK* (speaker biography)
9:15 Characterization of Nanostructured Materials (invited)
S.K. Sinha, *University of San Diego, US* (speaker biography)

8:30 Keynote - Nanotechnology for Cancer Prevention, Diagnosis and Treatment F
Session chair: Mansoor Amiji, Northeastern University
8:30 Challenges in Cancer Prevention, Diagnosis, and Therapy (invited)
J. Folkman, *Children's Hospital Boston, US* (speaker biography)
9:15 Delivery of Nano-medicine to Solid Tumors: Role of Tumor Physiology (invited)
R.K. Jain, *MGH, Harvard Medical School, US* (speaker biography)

8:30 WCM 1 - Bulk MOS Intrinsic models Roon
Session chair: Xing Zhou, Nanyang Technological University, Singapore
8:30 Carrier Generation and Recombination Currents At Interface Traps in Surface-Potential-Based MOS Transistor Compact Models (invited)
C-T Sah and B.B. Jie, *University of Florida, US*
9:00 Symbolic charge-based MOSFET model (invited)
C. Galup-Montoro and M.C. Schneider, *Federal University of Santa Catarina, BR*
9:30 Theory and Modeling Techniques used in PSP Model (invited)
G. Gildenblat, X. Li, H. Wang, W. Wu, A. Jha, R. van Langevelde, A.J. Scholten, G.D.J. Smit and D.B Klaassen, *Pennsylvania State University, US*

8:30 Clean and Controlled Environments - A4 Roon
Session chair: Paul Nesdore, Controlled Environments, US
8:30 Why Choose a Design/Build Contractor?
D. Kirkpatrick, *Western Environmental, US*
9:15 The Green Clean Laboratory
R.K. Schneider, *Clemson University, US*

8:30 Clean and Controlled Environments - B4 Roon
Session chair: Patrice Galvin, Controlled Environments, US
8:30 Critical Cleaning Using CO2 Snow
R. Sherman, *Applied Surface Technologies, US*
9:15 Chemical Filtration Strategies for the Control of Airborne Molecular Contamination
B. Stanley, *Purafil, US*

8:30 TechConnect Corporate Models and Needs Roon

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